DERIVATIVES OF 2-KETOPHENMORPHOLINE

BY
ELDRED WELCH
B.Ed., Southern Illinois Normal University, 1937
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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
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I. DERIVATIVES OF 2-KETOPHENMORPHOLINE

Introduction

Although a considerable number of compounds containing the 2-ketophenmorpholine nucleus have been prepared, only a few have been studied for their pharmacological action. The compounds studied have been N-alkyl derivatives[1] and compounds containing the arsonic acid grouping[2] in the aromatic nucleus. No derivative containing a 3-aminomethyl group has been reported in the literature, and, consequently no pharmacological study of this type of compound has been recorded.

One of the important methods for synthesizing 2-ketophenmorpholines consists in effecting ring closure of an *o*-hydroxy-α-haloacylanilide by means of alkali. The purpose of the present investigation was to study the extension of this general reaction in order to synthesize 2-ketophenmorpholine derivatives containing the diethylaminomethyl group in position-3.

Experimental and Discussion

If *o*-hydroxy-α-haloacylanilides with a more complex α-haloacyl group behave under the influence of alkali in the same way as do those with a simple α-haloacyl grouping, the following series of reactions should lead to 2-keto-3-diethylaminomethylphenmorpholine:

o-aminophenol + α-bromo-β-chloropropionyl chloride→ *o*-hydroxy-α-bromo-β-chloropropionanilide (I)

I + potassium hydroxide → 2-keto-3-chloromethylphenmorpholine (II)

II + diethylamine → 2-keto-3-diethylaminomethylphenmorpholine.

α-Bromo-β-chloropropionyl chloride, which was prepared by bromination of β-chloropropionyl chloride, reacted with *o*-aminophenol to produce *o*-hydroxy-α-bromo-β-chloropropi-

onanilide. The action of either aqueous or alcoholic potassium hydroxide on this compound did not cause a ring closure; instead there was formed *o*-hydroxy-α-bromoacrylanilide. Ozonization of this latter compound produced formaldehyde, identified as the dimethone derivative. Action of sodium hydroxide and benzoyl chloride with the same compound caused hydrolysis and the formation of the dibenzoyl derivative of *o*-aminophenol.

Diethylamine reacted with an acetone solution of *o*-hydroxy-α-bromoacrylanilide and of *o*-hydroxy-α-bromo-β-chloropropionanilide to produce *o*-hydroxy-α,β-di-(diethylamino)-propionanilide. Treatment of this last compound with sodium hydroxide and benzoyl chloride also lead to the dibenzoyl derivative of *o*-aminophenol.

The dihydrochloride of *o*-hydroxy-α,β-di-(diethylamino)-propionanilide was precipitated from an ether solution by passing in dry hydrogen chloride.

Starting with 2-amino-4-nitrophenol instead of *o*-aminophenol, reactions similar to those described above were carried out and analogous compounds were formed. These transformations were carried out according to the following sequence.

2-amino-4-nitrophenol $\rightarrow$ 2-hydroxy-5-nitro-α-bromo-β-chloropropionanilide $\rightarrow$ 2-hydroxy-5-nitro-α-bromoacrylanilide $\rightarrow$ 2-hydroxy-5-nitro-α,β-di-(diethylamino)-propionanilide$\rightarrow$dihydrochloride of 2-hydroxy-5-nitro-α,β-di-(diethylamino)-propionanilide.

Nitration of 2-ketophenmorpholine with concentrated nitric acid in the cold produced two mononitro derivatives. These were 2-keto-5-nitrophenmorpholine and 2-keto-6-nitrophenmorpholine.

Summary

α-Bromo-β-chloropropionyl chloride reacted with *o*-aminophenol to produce *o*-hydroxy-α-bromo-β-chloropropionanilide. Action of aqueous and of alcoholic potassium hydroxide on this compound lead to *o*-hydroxy-α-bromoacrylanilide. Diethylamine reacted with *o*-hydroxy-α-bromo-β-chloropropion-

anilide and with *o*-hydroxy-α-bromoacrylanilide to form *o*-hydroxy-α,β-di-(diethylamino)-propionanilide. This last compound formed a dihydrochloride when treated with dry hydrogen chloride in an ether solution.

Similar reactions were carried out starting with 2-amino-4-nitrophenol. The final product in this case was the dihydrochloride of 2-hydroxy-5-nitro-α,β-di-(diethylamino)-propionanilide.

2-Keto-5-nitrophenmorpholine and 2-keto-6-nitrophenmorpholine were produced by the nitration of 2-ketophenmorpholine.

II. ADDENDUM

MONOHYDROCHLORIDES OF THE *p*-AMINOBENZOATES OF *o*-DIALKYLAMINOMETHYLPHENOLS

Introduction

A very large number of compounds have been synthesized and tested for their local anaesthetic action since the introduction of novocaine. The latter has, however, retained its position as an inexpensive compound for producing local anaesthesia by injection.

At the present time, cocaine is still more widely used for topical anaesthesia than any other synthetic compound in spite of its toxicity and undesirable side effects. A good topical anaesthetic possessing low toxicity and no irritation could be very useful.

The present study had for its purpose the synthesis of some compounds which would be active topical anaesthetics. Specifically, it was proposed to carry out the Mannich reaction on a series of phenols and to convert the resulting dialkylaminomethylphenols to their *p*-aminobenzoates.

Experimental and Discussion

Phenols condense with formaldehyde and dialkylamines to produce dialkylaminomethylphenols.[3,4]. By this means it

has been possible to introduce one, two, or three dialkylaminomethyl groups into the phenol nucleus. It has been shown that if one of these groups is introduced into phenol, *o*-cresol or 2-methyl-4-ethylphenol, it enters the position ortho to the hydroxyl.[3,4]

In this study dimethylamine, diethylamine and piperidine were condensed with formaldehyde and phenol, *o*-cresol and 2,4-dimethylphenol in a water-alcohol solution, resulting in the formation of the following dialkylaminomethylphenols: 2-dimethylaminomethylphenol, 2-diethylaminomethylphenol, 2-piperidinomethylphenol, 2-dimethylaminomethyl-6-methylphenol, 2-diethylaminomethyl-6-methylphenol, 2-piperidinomethyl-6-methylphenol, 2-dimethylaminomethyl-4,6-dimethylphenol, 2-diethylaminomethyl-4,6-dimethylphenol and 2-piperidinomethyl-4,6-dimethylphenol. These compounds were all clear oily liquids, possessing little or no acidic properties as shown by the fact that they were difficultly soluble or were entirely insoluble in ten per cent sodium hydroxide solution.

The above aminophenols reacted with *p*-nitrobenzoyl chloride to produce white crystalline hydrochlorides of the *p*-nitrobenzoate esters. These esters were reduced with platinum and hydrogen to the monohydrochlorides of the *p*-aminobenzoates of the dialkylaminomethylphenols. These latter hydrochlorides would not dissolve in water or in two per cent boric acid solution to give clear solutions. There was always hydrolysis, resulting in a turbidity.

Bibliography

1. Hoffmann-LaRoche and Co., Ger. Patent 557111; Frdl. *19*, 1438.
2. Newberry, Phillips and Stickings, J. Chem Soc. *1928*, 3051.
3. Decombe, Compt. rend. *196*, 866 (1933).
4. Decombe, ibid. *197*, 258 (1933).
5. Bruson and MacMullen, J. Am. Chem Soc. *63*, 270 (1941).

VITA

The author was born near Norris City, Illinois, on December 2, 1912. He attended public school and high school in that town and was graduated from high school in 1930. He attended the Southern Illinois State Normal University during the school years 1932-1934 and 1935-1937, receiving the Bachelor of Education degree in June 1937. In September of that year, he entered the graduate school of the University of Illinois and received the degree of Master of Science in chemistry in February 1939. He held an assistantship in chemistry during the years 1937-1941.

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